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The Contribution of Physical Activity in Blood Glucose Concentration for People with Type 1 Diabetes

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Abstract: This paper addresses the problem of mathematical deconvolution for the estimation of unknown inputs in linear discrete-time state-space models. We apply our deconvolution algorithm to the modeling of blood glucose (BG) concentration for people with type 1 diabetes (T1D). We present a method using an activity tracking watch, a continuous glucose monitor and an insulin pump to study the effect of physical activity on BG concentration for people with T1D. The physical activity signatures are represented by an unknown input, also referred to as a "net effect". In addition, the net effect captures the unmodelled BG variations, eg. mismatches in meal estimation, and circadian metabolic variations. We test our method using data from a clinical study. We show the glucose net effect traces associated to physical activity for a specific patient during 20 consecutive days, and the glucose net effect traces associated to physical activity for eight subjects under identical conditions. The net effect signatures can be used to (i) reproduce experiments with different insulin administration strategies, (ii) build a physiological model of glucose-insulin dynamics able to simulate a physical activity in people with T1D, and (iii) design a model-based control algorithm able to predict the effect of physical activity on the blood glucose concentration.

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Keywords: Type 1 diabetes, Physical activity, Deconvolution, Disturbance estimation, Net effect.

1. INTRODUCTION

In people with type 1 diabetes (T1D), physical activity, and more generally a healthy lifestyle, is an essential complement to insulin therapy. It is recommended that patients with T1D undertake more physical activity than non-diabetic patients (Chimen et al. (2012)). Among other benefits, a regular physical activity improves blood glucose (BG) regulation in T1D, and reduces postprandial glucose excursions (Manohar et al. (2012)). However, the fear of hypoglycemia is the main barrier to the practice of a regular physical activity in T1D (Brazeau et al. (2008)), which may lead to prolonged hyperglycemia during and after physical activity. Therefore, it is hypothesized that being able to predict the effects of exercise on BG concentration may improve metabolic control and encourage the regular practice of physical activity.

From a control perspective, BG regulation during and after physical activity still remains a challenge (Breton (2008); Riddell et al. (2015)). Among other effects, physical activity results in an increased glucose uptake from the muscles, an increased glucose endogenous production,

a decreased insulin resistance, and a faster mobilization of subcutaneously administered insulin (Basu et al. (2014)). The glucose response to an exercise are highly dependent on the patient and the exercise intensity. While mild and moderate exercise usually require a decrease in basal insulin requirements and carbohydrates intake, intensive exercise may in some cases require a temporary increase in insulin basal rate to mitigate the increased endogenous glucose production from the liver (Turner et al. (2016)).

A number of models of T1D and simulators are available, for example Dalla Man et al. (2014); Wilinska and Hovorka (2014). Attempts have been made to model the effect of physical activity in T1D (Dalla Man et al. (2009); Duun-Henriksen et al. (2013); Schiavon (2014)). Nevertheless, no consensus exists yet as to the model form or parametrization necessary to encompass the variety of responses observed in clinical practices.

Accelerometers coupled with heart rate signal can detect physical activity and its intensity (Lazaro et al. (2016)), and the most recent devices able to track the physical activity may be sufficiently reliable to be used in clinical practice (Case et al. (2015)). For example, Breton et al. (2014) have shown that the integration of these devices

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into a closed-loop system (artificial pancreas) reduces the risk of hypoglycemia during and after an exercise in clinical studies.

The "net effect" is a technique that refers to deconvolution and can be used to estimate unmeasured disturbances (Prasath and Jørgensen (2009)). Del Favero et al. (2014) used deconvolution techniques to improve the accuracy of continuous glucose monitors (CGM) after calibration. Patek et al. (2016) used net effect to characterize the impact of CHO intake. Vettoretti et al. (2016) established that net effect can be used to some extent to replay simulations. However, the problem of deconvolution is usually an ill-posed problem, since several solutions can be found. One of the ways to circumvent this problem is to use regularization.

In this paper, we use the net effect to quantify the impact of physical activity on BG concentrations for patients with T1D. Periods of physical activity are identified by using an activity tracking watch. The use of net effect to collect BG variations caused by physical activity serves three purposes: (i) To recreate the clinical experiments under different conditions, (ii) to recreate physical activity in silico, and (iii) to design exercise-informed closed-loop algorithms.

Fig. 1 describes the procedure developed in this paper. A CGM measures the glucose concentration; a connected watch evaluates the level of physical activity (idle, mild, moderate or intensive); a CSII pump provides the history of insulin infusions; and the subject estimates the meal size. These data are provided to a discrete-time linear mathematical model and are used to identify the model parameters. The glucose net effect is determined as the solution of a convex quadratic program (QP).

The paper is structured as follows. Section 2 states and discusses the problem of deconvolution for linear time-invariant state space models. Section 3 describes the clinical protocol used to collect the insulin, glucose and physical activity data. In Section 4, we present the method for estimating a discrete-time linear model of the glucose-insulin dynamics and to compute the net effect. Section 5 presents and discusses the results on the clinical study data. Section 6 summarizes the main contributions of this paper.

2. PROBLEM FORMULATION

In this section, we state and discuss the model involved in deconvolution. We consider the discrete-time state space model

$$x_{k+1} = Ax_k + B_u u_k + B_w w_k, \quad (1a)$$

$$z_k = Cx_k, \quad (1b)$$

$$y_k = z_k + v_k, \quad (1c)$$

where x_k is the state vector. u_k is a vector representing the supposedly known input. z_k is the controlled variable. y_k is the measured output, and may be noise corrupted. $v_k \sim N_{iid}(0, R)$ is a white noise process. Here, we assume that A , B , B_w and C are known. The deconvolution problem considered in this paper consists in estimating the unknown input vector (also referred to as an unknown disturbance or as a net effect), w_k . The problem of de-

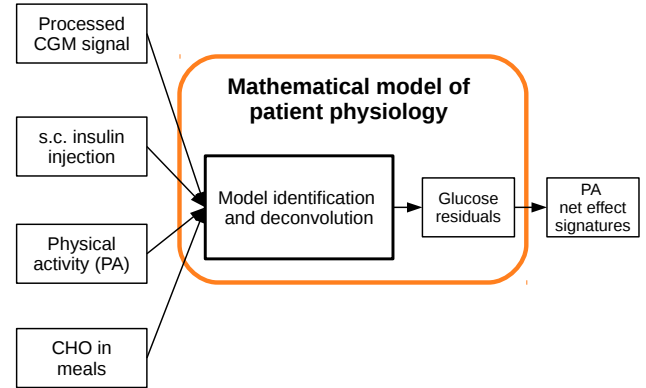


Fig. 1. Principle of net effect. Information about CGM measurements, sc. insulin, physical activity and meals are used to compute the net effect signatures associated to physical activity.

convolution is usually an ill-posed problem, and therefore requires the addition of a regularization term.

Remark 1. In this work, we made the choice to put the unknown disturbance on the state vector, x_k . The main reason behind this choice is that this disturbance should model an unknown glucose rate of appearance/disappearance. Alternatively, this term may be applied to the output vector, ie.

$$y_k = Cx_k + v_k + w_k. \quad (2)$$

Remark 2. The state space model (1) can also be derived from numerous models, such as a continuous-time transfer function model, a Box-Jenkins model, an ARX/ARMAX model, a stochastic differential equation (SDE) model, or a step/impulse response model.

2.1 Net effect estimation

The net effect, $w_k = w(t_k)$, is determined as a solution of a convex quadratic program. We consider the following optimization problem

$$\min_{e_k, w_k} \phi = \sum \|v_k\|_2^2 + \lambda_1 \|w_k\|_1 + \lambda_2 \|\Delta w_k\|_2^2, \quad (3a)$$

$$s.t. \quad (1). \quad (3b)$$

$\lambda_1 \|w_k\|_1$ and $\lambda_2 \|\Delta w_k\|_2^2$ are regularization terms. The weight on the 1-norm of w_k , λ_1 , penalizes non-sparse net effects, and is sometimes referred to as the least absolute shrinkage and selection operator (lasso) regression described eg. in Tibshirani (1996). The weight on the 2-norm of Δw_k , λ_2 , ensures small variations on the net effect vector.

By introducing the slack variables, s_k , we can reformulate the optimization problem (3) as the constrained convex quadratic program

$$\min_{v_k, w_k, s_k} \sum \|v_k\|_2^2 + \lambda_1 s_k + \lambda_2 \|\Delta w_k\|_2^2 \quad (4a)$$

$$s.t. \quad (1), \quad (4b)$$

$$-s_k \leq w_k \leq s_k, \quad (4c)$$

$$s_k \geq 0. \quad (4d)$$

The term $\lambda_1 s_k$ in (4a) and the inequality constraints (4c-4d) give the two cases for the optimal value of the slack variables s_k

$$\begin{cases} s_k = w_k & \text{if } w_k \geq 0, \\ s_k = -w_k & \text{if } w_k < 0. \end{cases} \quad (5)$$

Consequently, the numerical solution of (4) yields the net effect w_k .

3. COLLECTION OF CLINICAL DATA

Data were collected during an IRB-approved clinical trial NCT02558491 (<http://www.clinicaltrials.gov>) at the University of Virginia from 15 study subjects on CSII and 10 study subjects on multiple daily injections (MDI), ie. insulin pen, all having been diagnosed with type 1 diabetes for at least six months. Each patient experienced two identical outpatient admissions of 48 hours (separated by four weeks or more), experiencing both meal and exercise challenges designed to induce glucose variability. Each subject was randomized into experiencing either "usual care" first or optimized individualized decision support. Decision support parameters were computed from "open-loop" data including CGM (blinded if not already a CGM user), insulin delivery, meals (with carbohydrate estimates), and physical activity. In addition to CGM data, meal and insulin data were collected.

4. NET EFFECT

A number of unknown factors may affect BG concentrations in T1D, including (i) variability in insulin sensitivity, caused by eg. stress, illness, menstrual cycles, physical activity, (ii) variations in insulin transport after physical activity, (iii) under- or overestimating the CHO content of a meal (Brazeau et al. (2013)), (iv) the difference in meal dynamics, related for instance to the fat content of the meal.

In this section, we present our net effect algorithm to capture the effect of these sources of uncertainty, and in particular physical activity on BG concentration. This net effect will capture the variations in glucose utilization during physical activity that matches the CGM and insulin administration data.

We use an extended version of the minimal model of glucose-insulin dynamics published in Bergman et al. (1979), referred to as the subcutaneous oral glucose minimal model (SOGMM). The SOGMM model is presented in Patek et al. (2016). This model includes the effect of subcutaneously administered insulin, CHO intakes, and a term that describes the effect of factors such as physical activity and model-patient mismatches. The continuous-time model is individualized using the patient's body weight and two identified parameters, namely the insulin gain and one time constant.

We linearize the continuous-time model of CHO absorption and convert it into a discrete-time transfer function model. Similarly, we use a second-order linear transfer function model to describe the effect of subcutaneous insulin infusion on BG concentration. Using these transfer function models, we compute the glucose net effect as the solution of a constrained optimization problem.

4.1 Mathematical model

In the SOGMM model, the BG concentration, $G(t)$ [mg/dL], is given by

$$\dot{G}(t) = -\left(\frac{1}{\tau_G} + X(t)\right)G(t) + \frac{G_b}{\tau_G} + \frac{R_a(t)}{V_g} + w(t), \quad (6)$$

in which τ_G [min] is a time constant associated to glucose. $w(t)$ [mg/dL/min] is an additional input to BG concentration (the net effect). G_b [mg/dL] is the basal BG concentration. $X(t)$ [1/min] is the proportion of insulin in the remote compartment.

4.2 Continuous-time transfer function models

The full continuous-time model of glucose dynamics expressed in the Laplace domain is

$$G(s) = H_1(s)\Omega(s) + H_2(s)U_I(s) + H_3(s)W(s) + H_4(s)E(s). \quad (7)$$

The following continuous-time transfer function model describes the dynamics between the Laplace transforms of the ingested CHO, $\Omega(s)$, and the blood glucose concentration, $G(s)$

$$H_1(s) = \frac{G(s)}{\Omega(s)} = \frac{K_G}{(\tau_{CHO}s + 1)^2(\tau_G s + 1)}. \quad (8)$$

The time constants, τ_{CHO} and τ_G , are fixed to 40 and 100 minutes, respectively (Hovorka et al. (2004); Patek et al. (2016)). The gain, K_G , is (Patek et al. (2016))

$$K_G = \frac{f}{BWV_G}. \quad (9)$$

f represents the bioavailability of CHO. V_G is the glucose distribution volume. The patient's body weight, BW , is individualized for each patient. Table 1 summarizes the numerical values of the fixed parameters used for identification. The transfer function model (8) would be similar to a linearization of the glucose compartment and the meal compartments.

We propose here a second-order transfer function model, $H_2(s)$ from subcutaneously administered insulin to blood glucose

$$H_2(s) = \frac{K_I}{(\tau_I s + 1)^2}, \quad (10)$$

in which the insulin gain, K_I , and the time constant, τ_I , are identified. Although this transfer function model is of a lower order than the linearization of the SOGMM, we showed in our previous work that this second order model structure offered the best trade-off between identifiability and closed-loop performance (Boiroux et al. (2015); Hagdrup et al. (2016)).

We also consider a transfer function model of blood glucose

$$H_3(s) = \frac{G(s)}{W(s)} = \frac{\tau_G}{\tau_G s + 1}. \quad (11)$$

This transfer function describes all the dynamics that are not modelled by the transfer functions (8) and (10). It includes the metabolic variations in insulin sensitivity, the mismatches in meal and insulin dynamics, inaccuracies in carbohydrate counting, physical activity etc. The term $W(s)$ is not known in the Laplace domain, but is estimated in its discrete-time form, as shown in Section 2.1.

Table 1. Numerical values of the fixed parameters.

Parameter	Unit	Value
f	-	1
τ_G	min	100
τ_{CHO}	min	40
V_G	dL/kg	1.6

We consider a stochastic term in the transfer function model of blood glucose, which is

$$H_4(s) = \frac{G(s)}{E(s)}. \quad (12)$$

This transfer function includes all the other glucose variations.

4.3 Discrete-time linear model

We discretize the continuous-time model (7) into discrete-time Box-Jenkins model using a zero-order hold (ZOH) parametrization on the inputs. The resulting discrete-time Box-Jenkins model is

$$y(t_k) = \frac{B_1(q^{-1})}{A_1(q^{-1})}u_I(t_k) + \frac{B_2(q^{-1})}{A_2(q^{-1})}u_M(t_k) + \frac{B_3(q^{-1})}{A_3(q^{-1})}w(t_k) + e(t_k). \quad (13)$$

The sampling time is 5 minutes. $A_1(q^{-1})$, $A_2(q^{-1})$, $A_3(q^{-1})$, $B_1(q^{-1})$, $B_2(q^{-1})$ and $B_3(q^{-1})$ are polynomials of appropriate orders. $w(t_k)$ [mg/dL/min] describes the effect of physical activity and other unmodelled phenomena on blood glucose concentration. $e(t_k)$ is assumed to be a white noise process. The discrete-time Box-Jenkins model (13) can be realized as a multiple input single output autoregressive moving average with exogenous inputs (ARMAX) model

$$\bar{A}(q^{-1})y(t_k) = \bar{B}(q^{-1})U(t_k) + \bar{C}(q^{-1})e(t_k), \quad (14)$$

in which $U(t_k)$ represents the three inputs, ie. the insulin injections, $u_I(t_k)$, the meal intakes, $u_M(t_k)$, and the net effect, $w(t_k)$. It is defined as

$$U(t_k) = \begin{bmatrix} u_I(t_k) \\ u_M(t_k) \\ w(t_k) \end{bmatrix}. \quad (15)$$

The polynomials $\bar{A}(q^{-1})$, $\bar{B}(q^{-1})$ and $\bar{C}(q^{-1})$ are

$$\bar{A}(q^{-1}) = A_1(q^{-1})A_2(q^{-1})A_3(q^{-1}), \quad (16a)$$

$$\bar{B}(q^{-1}) = \begin{bmatrix} B_1(q^{-1})A_2(q^{-1})A_3(q^{-1}) \\ A_1(q^{-1})B_2(q^{-1})A_3(q^{-1}) \\ A_1(q^{-1})A_2(q^{-1})B_3(q^{-1}) \end{bmatrix}^T, \quad (16b)$$

$$\bar{C}(q^{-1}) = A_1(q^{-1})A_2(q^{-1})A_3(q^{-1}). \quad (16c)$$

4.4 Parameter identification

We use a least squares to identify the deterministic model of glucose-insulin dynamics

$$G(s) = H_1(s)\Omega(s) + H_2(s)U_I(s). \quad (17)$$

We identify the gains, K_I and K_G , and the time constant associated to sc. insulin absorption, τ_I . The deterministic part of (13)

$$G_d(t_k) = \frac{B_1(q^{-1})}{A(q^{-1})}u_I(t_k) + \frac{B_2(q^{-1})}{A(q^{-1})}u_M(t_k) \quad (18)$$

describes the effects of the insulin infusion rate, $u_I(t_k)$, and the ingested meals, $u_M(t_k)$, on the BG concentration, $G(t_k)$.

The discrete-time transfer functions, $B_1(q^{-1})/A(q^{-1})$ and $B_2(q^{-1})/A(q^{-1})$, are obtained by discretization of the continuous-time transfer functions $H_1(s)$ and $H_2(s)$ in (17), respectively.

4.5 State space realization

The ARMAX model (14) may be represented as a discrete-time state space model in innovation form

$$x_{k+1} = Ax_k + B_I u_{I,k} + B_M u_{M,k} + B_w w_k + K e_k, \quad (19a)$$

$$y_k = Cx_k + v_k, \quad (19b)$$

where x_k is the state vector. $u_{I,k}$, $u_{M,k}$ and w_k are the insulin injections, the meal intake and the net effect, respectively. $v_k \sim N_{iid}(0, R)$ is a white noise process. The innovation, e_k , is

$$e_k = y_k - \hat{y}_{k|k-1}. \quad (20)$$

We realize the state space model (19) such that the matrices A , B_I , B_M , B_w and K are in observer canonical form (Boiroux et al. (2012)).

5. RESULTS AND DISCUSSION

In this section, we present net effect signals for the eight subjects undergoing the same physical activity under the same experimental conditions, and show net effect traces for a specific subject having a regular physical activity over a 20-day period. For each subject, we compute the net effect signal as described in section 4 and isolate the timings of physical activity by using the information provided by the activity tracker. The physical activity time is defined when the subject is either "moderately active" or "very active" according to the activity tracking watch.

Fig. 2 shows the reconstructed CGM data using the discrete-time linear model (13) and the net effect blood glucose variations computed as the solution of (4) for a period of 24 hours. The figure shows that this formulation is able to correctly reconstruct the CGM signal by using a linear physiological model of glucose-insulin dynamics and a net effect term capturing the variations in blood glucose that are not included in the linear model.

5.1 Inter-patient variability

Fig. 3 shows the mean and standard deviation of the glucose after the beginning of a physical exercise. We extracted the net effect signatures associated to the standardized physical activity included in the control outpatient admission (no use of the decision support system). The time, duration and intensity are identical for the 8 considered subjects. The figure shows that the variability in the net effect values is high for the considered subjects at the beginning of the physical activity. In some cases, intensive physical activity may increase BG concentration. This increase in BG concentration may be caused by an increase in endogenous glucose production from the liver, or by the absorption of a snack before the exercise onset. The maximum glucose uptake happens approximately 20 to 30 minutes after the beginning of the physical activity.

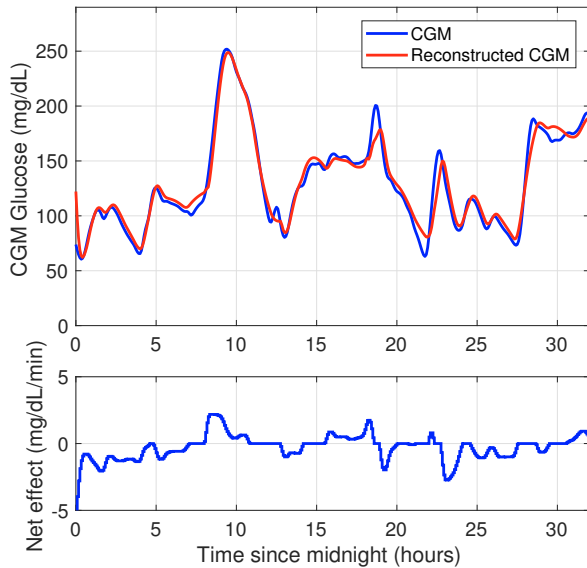


Fig. 2. Example of reconstruction of the CGM signal using the model (14).

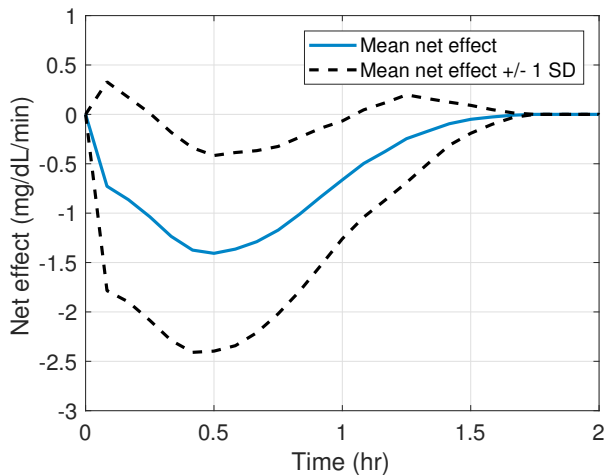


Fig. 3. Net effect signatures associated to physical activity for the 8 subjects during the control period.

5.2 Net effect signatures for a specific subject

Fig. 4 illustrates the processed glucose concentration trace measured by a CGM, exercise times and the glucose net effect for a period of 36 hours. Other variations in net effect can be due to intra-patient metabolic variations, CGM noise or longer-term effects of physical activity.

Fig. 5 shows the net effect signatures associated to physical activity for a specific subject. For illustration purpose, we chose a subject having a regular physical activity and no extended period of missing CGM data. The net effect signatures have been collected for a period of 20 consecutive days. These net effect signatures can be used in a control algorithm to predict the effect of physical activity and to improve the safety of glucose regulation (Patek (2010)).

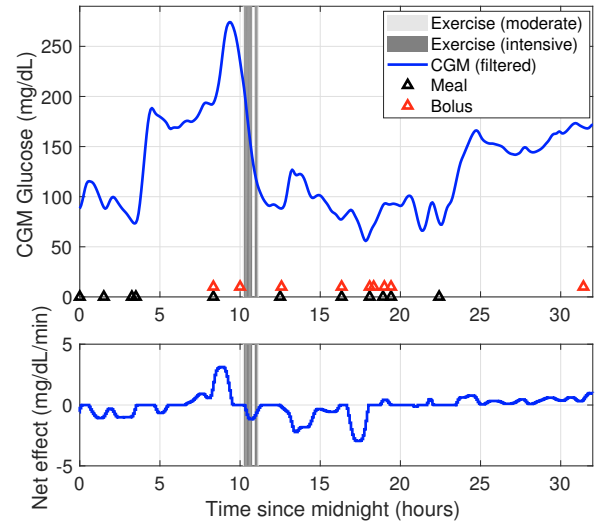


Fig. 4. Example of net effect for a 32-hour period.

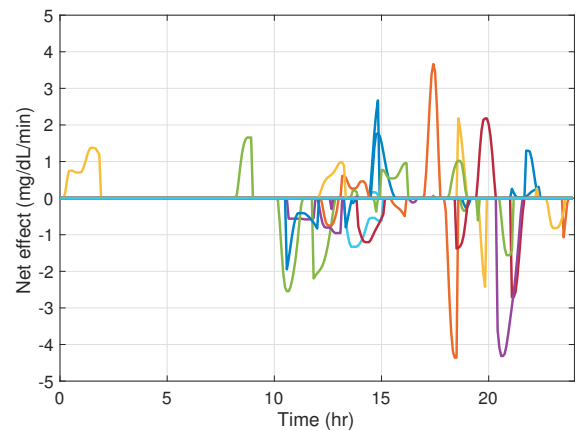


Fig. 5. Net effect signatures associated to physical activity for a specific subject. The net effect signatures have been collected for a period of 20 consecutive days.

6. CONCLUSION

This paper presents a method based on mathematical deconvolution to quantify the glucose variations that are not represented in a model. By combining this with a watch tracking physical activity, we are able to isolate the glucose variations associated to physical activity. One of the limitations of this study is that physical activity is often preceded by a meal intake and/or an insulin bolus, thus making it difficult to distinguish between the variations in glucose concentration due to physical activity and the variations in glucose concentration due to meal and/or insulin bolus.

However, the fact that physical activity is usually coupled with a meal intake and/or an insulin bolus is still useful to predict the glucose variations during and after exercise. Moreover, meals, insulin delivery, sensor drifts etc. limit our ability to evaluate the long-lasting effects of exercise through net effect.

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